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Original Research Article

10-year outcomes after off-pump vs on-pump coronary artery bypass grafting. Insights from the Arterial Revascularization Trial.

Running Title: off-pump vs on-pump surgery

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Abstract

Objectives: We performed a post hoc analysis of the Arterial Revascularization Trial to compare 10-year outcome after off-pump vs on-pump surgery.

Methods: Among 3102 patients enrolled, 1252 (40% of total) and 1699 patients received off-pump and on-pump surgery (and 151 were excluded because of other reasons); 2792 (95%) patients completed 10-year follow-up. Propensity matching and mixed effect Cox model were used to compare long term outcomes. Interaction term analysis was used to determine whether bilateral internal thoracic artery grafting was a significant effect modifier.

Results: 1078 matched pairs were selected for comparison. A total of 27 patients (2.5%) in the off-pump group required conversion to on-pump surgery. The off-pump and on-pump group received a similar number of grafts (3.2±0.89 vs 3.1±0.8; P=0.88). At 10 years, when compared to on-pump, there was no significant difference in death (adjusted HR for odd-pump: 1.1; 95%CI 0.84-1.4; P=0.54) or the composite of death, myocardial infarction, stroke and repeat revascularization (adjusted HR 0.92; 95%CI 0.72-1.2; P=0.47). However, off-pump surgery performed by low volume off-pump surgeons was associated with a significantly lower number of grafts, increased conversion rates and an increased cardiovascular death (HR 2.39; 95%CI 1.28-4.47; P=0.006) when compared to on-pump surgery performed by “on-pump only” surgeons.

Conclusions: The present findings showed that in the Arterial Revascularization Trial off-pump and on-pump techniques achieved comparable long-term outcomes. However, when off-pump surgery was performed by low volume surgeons, it was associated with a lower number of grafts, increased conversion and a higher risk of cardiovascular death.

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Ultra-mini abstract

In experienced hands, off-pump surgery can achieve long term outcomes comparable to those observed after on-pump surgery and can therefore be considered a valid alternative to on-pump to reduce surgical morbidity. The choice of bilateral vs. single internal thoracic artery grafts should not influence the decision to adopt the off-pump technique.

Introduction

Whether off-pump coronary artery bypass graft (CABG) surgery is as safe and effective as on-pump surgery remains one of the most controversial areas of cardiac surgery.[1] Some randomized controlled trials (RCT) have found increased mortality following off-pump surgery[1,2] but limited surgeon off-pump experience has been advocated to explain these results.[2] On the other hand, off-pump has been shown to achieve results comparable to on-pump surgery when performed by experienced surgeons.[3,4] However, available RCTs are limited by relatively short follow-up duration (5 years) and differences in clinical outcomes may become evident with longer follow-up duration.[5]

Moreover, available data comparing off-pump and on-pump surgery were based on a single internal thoracic artery graft (SITA) supplemented by saphenous vein grafts (SVGs).[2–4] There is growing concern that off-pump surgery is associated with a significantly higher graft failure rate when SVGs but not arterial grafts are used.[6] Therefore, it has been suggested that a more extensive use of arterial grafts including bilateral internal thoracic artery (BITA) grafts should be adopted during off-pump surgery.[6,7]

The Arterial Revascularization Trial (ART) was designed to compare 10-year survival after BITA versus SITA grafting and the final results have recently reported.[8] In the ART, the choice of off-pump versus on-pump was based on the surgeon's preference in accordance with their clinical expertise. As such, the ART trial may provide useful insights into the long-term effect of off-pump surgery when performed by surgeons who use it routinely in clinical practice. Moreover, the ART trial can provide further information regarding the role of BITA vs. SITA grafting in patients undergoing off-pump surgery. We performed a post-hoc analysis to compare 10-year outcomes after off-pump vs on-pump surgery and the effect of BITA vs. SITA grafting.

Materials and Methods

The present study is a post hoc retrospective analysis of 10-year outcomes of the ART trial. The study was approved by an institutional review committee and the subjects gave informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study adheres to the principles set forth in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). In the ART, the choice of off-pump versus on-pump surgery was based on individual surgeon discretion in accordance with their routine clinical practice. The off-pump versus on-pump strategy adopted was available for all patients enrolled.

Among all patients enrolled in the ART (n = 3102, from 2004 to 2007), we excluded a total of 151 patients including those who did not undergo surgery (n = 24), incomplete information regarding the use of cardiopulmonary bypass and myocardial protection strategy (n=6), patients who received on-pump beating heart surgery (n = 23) and 98 patients who received cross clamp fibrillation. The present analysis compared 1252 patients who underwent off-pump surgery versus 1699 patients who underwent on-pump with cardioplegic arrest. Off-pump surgery requiring intraoperative conversion to on-pump was included in the off-pump group in the primary analysis (**Supplementary Figure 1**).

Trial Design

The ART was approved by the institutional review board of all participating centers, and informed consent was obtained from each participant. The protocol for the ART has been published.[9] Briefly, the ART is a 2-arm, randomized multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to SITA or BITA grafting. Eligible patients were those with multivessel coronary artery disease undergoing coronary artery bypass grafting, including patients requiring urgent treatment. Only patients requiring emergency treatment (refractory myocardial ischemia/cardiogenic shock) and patients requiring single grafts or redo surgery were excluded.

Follow-up

Questionnaires were sent to study participants by mail at 12 months and then every year after surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the questionnaire's arrival and to ask them about medications, adverse events, and health services resource use. A total of 2792 (95%) patients completed 10-year follow-up. Median follow-up time was 10.0 [interquantile range 9.3-10.0] years.

Study Outcomes

The 2 strategies were compared in terms of hospital and 10-year outcomes. The primary endpoint was all-cause mortality. We also investigated the incidence cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, and repeat revascularization and a combined endpoint of death, MI, stroke and repeat revascularization. Adverse events were adjudicated blind to surgical procedure by a member of the Clinical Event Review Committee.

Outcomes Definitions

Death was classified into cardiovascular and non-cardiovascular, when possible, using autopsy reports and death certificates. Congestive heart failure, arrhythmia or MI, pulmonary embolus, and dissection were considered cardiovascular causes of death. MI was diagnosed when 2 of the following 3 criteria were present: (1) unequivocal electrocardiogram changes; (2) elevation of cardiac enzyme(s) above twice the upper limit of normal or diagnostic troponin increases; and (3) chest pain typical for acute MI that lasted more than 20 minutes. Cerebro-vascular accident (CVA) was defined as new neurologic deficit evidenced by clinical signs of paresis, plegia, or new cognitive dysfunction including any mental status alteration lasting more than 24 hours or evidence on computed tomography or magnetic resonance imaging scan of recent brain infarct (<6 months). Repeat revascularization was defined as coronary bypass surgery or percutaneous coronary intervention performed after trial procedure. Acute kidney injury was defined as a 0.3 mg/dL (≥26.5 mmol/L) creatinine increase from baseline within 48 hours of surgery.

Statistical Analysis

Multiple imputation (m = 3) was used to address missing data. Rubin's method was used to combine results from each of the imputed data sets (Amelia R package).[10] Because of the lack of randomization with regard to receiving off-pump, a propensity score was generated for each patient from a multivariable logistic regression model based on pretreatment covariates listed in **Table 1**. Pairs of patients were derived using greedy 1:1 matching with a caliper of width of 0.005 (nonrandom R package). As the sample size of the two groups was comparable as well as the prevalence of most pre-matching features, we used a more restrictive value than the 0.2 standard deviation of the logit of PS in order to obtain comparable pairs. The quality of the match was assessed by comparing selected pretreatment variables in propensity score–matched patients using the standardized mean difference, with an absolute standardized mean difference (SMD) of greater than 0.10 taken to represent meaningful covariate imbalance.[11] McNemar's test and paired t test were used to assess the statistical significance of the risk difference for hospital outcomes. In absence of competing events, the 1 minus Kaplan-Meier estimator was used to calculate cumulative incidence function with its relative 95% standard error while the Fine and Gray approach was used to account for presence of competing risk on a subdistribution hazard function.

Event rates for 10-years outcomes were calculated according to Kaplan–Meier estimates and were compared using a stratified log-rank test. The treatment effect on the 10-year outcomes was investigated by means of mixed effect Cox regression models stratified by matched pairs (coxme R package). This approach accounts for the within-pair homogeneity by allowing the baseline hazard function to vary across matched sets.[11] Individual surgeon ID was used as a random effect to account for any clustering effect due to different individual surgeons. Risk competing framework was used to estimate the treatment effect on non-fatal events and cardiovascular death. The Schoenfeld residuals test was used to test the independence between residuals and time, and thus to test the proportional hazards assumption in Cox models. Treatment effect was reported as hazard ratio (HR) and 95% confidence interval (95%CI).

As sensitivity analysis, the treatment effect was re-estimated by further adjustment for medications at discharge. Subgroup and interaction term analyses were performed to investigate whether BITA vs SITA grafting was a potential effect modifier in the comparison between off-pump vs. on-pump surgery. We also investigate the interaction between off-pump vs on-pump surgery and the use of the radial artery (RA) and the use of multiple arterial grafting (MAG) defined as the use of 2 or more arterial grafts.

To account for the potential influence of individual surgeons' off-pump experience, we compared off-pump vs on-pump surgery stratified by surgeon expertise in off-pump surgery. The number of off-pump procedure within the trial was used as proxy for individual surgeon expertise in off-pump surgery. The cut-off to define high off-pump volume surgeons corresponded to the 75th percentiles of total number of off-pump cases performed by each off-pump surgeon (10 off-pump surgeries). Five groups were compared: 1) off-pump surgery performed by “high off-pump volume” surgeon; 2) off-pump surgery performed by “low off-pump volume” surgeon; 3) on-pump surgery performed by “high off-pump volume” surgeon; 4) on-pump surgery performed by “low off-pump volume” surgeon; 5) on-pump surgery performed by “on-pump only” surgeon. The treatment effect on outcomes of interest was investigated using mixed Cox models using individual surgeon as random effect (random intercept) and all baseline characteristics as fixed effect. On-pump surgery performed by “on-pump only” surgeons was considered as refence group. To investigate the effect of surgeon off-pump volume, the original sample was used. A p-value less than 0.05 was considered statistically significant. All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

The unmatched sample consisted of 1699 and 1252 patients undergoing off-pump vs on-pump surgery respectively (**Supplementary Table 1, Supplementary Table 2**). Overall, the off-pump group presented a trend toward a higher risk profile including increased creatinine level and higher prevalence of unstable angina. The prevalence of 3 vessel disease was also higher among off-pump patients and the quality of native vessels tended to be worse. BITA grafts were more likely to be used in the off-pump group while a radial artery was more likely to be used in the on-pump group. Propensity score matching identified 1078 pairs (total matched sample = 2156) for final comparison, balanced for all baseline characteristics (SMD<0.10, **Table 1**) and propensity score distribution was comparable between the two matched groups (**Figure 1**).

Hospital outcomes

In-hospital outcomes in the matched sample are reported in **Table 2**. A total of 27 patients (2.5%) in the off-pump group required conversion to on-pump surgery. The off-pump and on-pump group received a comparable number of total grafts (3.2±0.89 vs 3.1±0.8; P=0.88). Off-pump surgery resulted in a lower rate of transfusion and a lower incidence of post-operative atrial fibrillation and peri-operative MI with a marginally non-significant reduction of CK-MB release postoperatively. In-hospital mortality, stroke and repeat revascularization was comparable between the two groups. Patients undergoing off-pump surgery were more likely to be discharged on dual antiplatelet therapy, but they were less likely to receive statins (**Supplementary Table 3**).

10-year outcomes

10-year outcomes and treatment effect are summarized in Table 3. The incidence of all-cause mortality and the composite of death, MI, stroke and revascularization was 232 (21.5%) vs 215 (19.9%) and 355 (32.7) vs 356 (33.0) in the off-pump and on-pump group respectively (**Figure**

2). When compared to on pump, off-pump surgery was not associated with increased risk of all-cause death (HR 1.1; 95%CI 0.84-1.4; P=0.47) nor the composite of death, MI, stroke and revascularization (HR 0.92; 95%CI 0.72-1.2; P=0.47). No significant differences were recorded for composite outcome individual components (**Figure 3**). The equipoise between the two groups persisted after adjusting for medications at discharge.

When the analysis was stratified by BITA vs SITA grafting, the presence of BITA vs. SITA grafting did not significantly influence the comparison between off-pump and on-surgery for all outcomes of interest (**Table 4, Figure 4**). However, when compared to on-pump, off-pump surgery was associated with a non-significant excess of cardiovascular deaths when SITA (off-pump vs on-pump HR 2.0174; 95%CI 1.1-3.7) but not BITA grafts (off-pump vs on-pump HR1; 95%CI 0.45-2.3) were used (interaction P=0.21). Off-pump and on-pump surgery were comparable in terms of 10-year mortality and incidence of major adverse cardiac and cerebrovascular outcomes regardless the use of the RA (**Supplementary Figure 2**) or any multiple arterial grafting configuration (**Supplementary Figure 3**).

A total of 159 participating surgeons were involved (**Supplementary Figure 4**). Ninety-eight surgeons performed on-pump only while off-pump was performed by 61 surgeons including 21 surgeons who performed off-pump only. For 133 patients (59 off-pump, 74 on-pump), no information on participating surgeon was available and these were not included in this analysis. High off-pump volume surgeons were defined those performing over the 75th percentile. Based on the identified cut-off of least 10 off-pump procedures, 21 surgeons were classified as high volume off-pump performing 1075 procedures and the remaining 40 surgeons were classified as low-volume off-pump performing a total of 118 off-pump procedures. A total of 98 surgeons performed on-pump only. Patients characteristics, hospital outcomes stratified for off-pump vs. on-pump surgery and surgeon off-pump volume are summarized in **Supplementary Table 4 and 5**. The use of BITA vs SITA graft (as treated) according to off-pump surgeon volume is summarized in **Supplementary Table 6**. High volume off-pump surgeons were more likely to perform BITA grafting. For low-volume off-pump surgeons, the use of off-pump technique did not influence the use of BITA or SITA grafting. Surgeons only performing on-pump surgery had the lowest rate of BITA grafting usage.

10-year outcomes and adjusted treatment effect estimation on these outcomes stratified by surgeon off-pump volume are presented in **Supplementary Table 7 and 8**. When performed by low volume off-pump surgeons, off-pump surgery resulted in a significantly lower number of grafts and higher conversion rates while this trend was not observed when off-pump was performed by high volume off-pump surgeons. When compared to on-pump surgery performed by "on-pump only" surgeons, off-pump surgery performed by low volume off-pump surgeons was associated with a significantly increased risk-adjusted incidence of cardiovascular death (HR 2.39; 95%CI 1.28-4.47; P=0.006) and increased risk of late stroke (HR 3.97; 95%CI 1.81-7.95; P<0.001) at 10 years. No difference in long term outcomes were demonstrated for off-pump surgery performed by high volume off-pump surgeons and for on-pump surgery performed by high and low volume off-pump surgeons. BITA vs SITA grafting was not an effect modifier in the comparison between off-pump vs. on-pump surgery.

Discussion

The main finding of the present post-hoc analysis of the ART was that at 10 years, off-pump and on-pump surgery were associated with comparable outcomes including all-cause mortality and the composite of death, MI, stroke and repeat revascularization. When compared to on-pump, off-pump surgery was associated some advantage in terms of hospital outcomes including a lower rate of transfusion and post-operative atrial fibrillation.

The use of SITA or BITA grafts was not found to be a significant effect modifier in the comparison between off-pump vs. on-pump surgery. It has been suggested that off-pump surgery may increase the risk of SVG failure[6] without affecting graft patency of arterial conduits including BITA grafts. However, other reports have shown that both arterial and vein grafts durability is not reduced when off-pump surgery is performed by experienced surgeons.[12] Available randomized comparative studies on long-term survival after off-pump vs. on-pump surgery included mainly procedure with SITA grafting.[2–4] Observational studies have suggested that off-pump surgery with multiple arterial grafts but not vein grafts provides long-term outcomes comparable with those observed on-pump surgery with multiple arterial grafts.[7]

Our findings suggest that off-pump surgery can safely performed regardless the use of BITA or SITA grafts. As the choice to perform on-pump or off-pump was based on individual surgeon's preference, the overall experience in off-pump surgery in the ART was likely to be adequate and this can explain the equipoise between the two techniques regardless the graft selection adopted.[12] However, it must be noticed that although not statistically significant, off-pump surgery was associated with a non-significant excess of cardiovascular deaths in patients who received SITA graft but not in those with BITA grafts and this observation requires further investigation.

We further analyzed the effect of off-pump surgery according to individual surgeon off-pump volume. When compared to on-pump performed by on-pump only surgeons, off-pump surgery performed by low-volume off-pump surgeons was associated with a significantly lower number of grafts and significantly increased risk of on-pump conversion, cardiovascular death and late stroke at 10 years. On contrary, off-pump surgery performed by high off-pump volume surgeon was associated with comparable number of grafts and 10 years outcomes.

Off-pump volume at individual surgeon or hospital level are intuitive measures of ‘‘expertise’’ and a proxy of enhanced safety and quality[5] and studies suggesting an increased risk of late mortality after off-pump surgery have been criticized by those who believe that surgeon experience plays a major role in determining outcomes. In the ROOBY trial,[2] 53 participating surgeons enrolled an average of only 8 patients per year during the study period and had unacceptably high conversion rates to on-pump surgery (12%) and incomplete revascularization (18%). Moreover, in 60% of the cases, a resident was the primary surgeon. These aspects might have contributed to the higher mortality observed in the off-pump group. In the CORONARY trial[3] where each procedure was performed by a surgeon who had expertise in the specific type of surgery (completion of>100 cases of the specific technique, off-pump or on-pump), the difference in terms of number of grafts (3.0 vs 3.2) and incidence of incomplete revascularization (11.8% vs 10.0%) were only marginal and off-pump and on-pump surgery showed similar 5-year outcomes, including mortality with both techniques. Similar results were observed in the German off pump CABG trial in elderly patients study,[4] where surgeons were established experts with an average of 514 OPCAB procedures (median, 322) performed, and where no significant differences between OPCAB and on-pump outcomes were found.

A potential limitation of studies supporting the equipoise between the two techniques is the limited follow-up duration of 5 years and the ART trial, with 10-year follow-up, can provide further insights into the long-term comparison between off-pump vs on-pump surgery. Off-pump surgery was performed at the individual surgeon’s discretion. Furthermore it is likely that the overall off-pump experience in the ART trial was adequate as witnessed by a similar number of grafts in the off-pump and on-pump groups, the very low off-pump to on-pump conversion rate and the equipoise between the two groups at 10 years. This hypothesis is supported by other reports from high off-pump volume centers.[13]

Of note, the number of grafts performed with off-pump surgery and the incidence of conversion from off-pump to on-pump surgery in the ART trial was lower than those reported in other series.[2] Finally, we also found that off-pump surgery was also associated with a non-significant reduction of myocardial enzymes and a lower rate of peri-operative MI as defined by the study protocol. It is well recognized that off-pump surgery is associated with a lower release of myocardial enzymes,[14] but the clinical relevance of this observation remains unclear (**Supplementary Table 8**) also in view of comparable long-term outcomes between the two techniques. Moreover, the definition of perioperative MI after myocardial revascularization remains controversial.[15]

Limitations

The main limitation of the present study is its observational nature. The propensity technique can adjust only for measurable and included variables, and we cannot exclude a selection bias based on a nonmeasurable “eye-balling,” including the quality of the targets. We had no information on specific surgeon off-pump expertise, and we used the total number of off-pump procedures performed in the ART as a surrogate of off-pump expertise. We had no information on reasons for preferring off-pump over on-pump and vice versa across surgeon subgroups. The number of off-pump surgeries performed by low off-pump volume surgeons was relatively small thus increasing the risk of type I error. Therefore, subgroup analysis based on surgeon off-pump volume should be considered only as descriptive and hypothesis generating.

It should also be noted by today's standards that the ART population might be considered a relatively low risk subset of CABG patients (although the only formal exclusion criteria were evolving myocardial infarction, redo surgery or the need for a single graft). It is possible that a difference between the two techniques could exist in patients at higher surgical risk.

In conclusion, we found that when performed by experienced surgeons, off-pump was as safe and effective as on-pump surgery at long term follow-up regardless the use of BITA vs. SITA grafts. In the current era, an increasing number of patients with a high-risk profile are being referred for surgical revascularization, and off-pump surgery represents an attractive strategy to potentially reduce operative morbidity. However, the unique technical challenges of off-pump surgery may lead to poorer outcomes during each surgeon's ‘‘learning curve’’ and this further emphasizes the need for recognition of off-pump surgery as a subspecialty with a formally structured training program.[16]

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Central Message:

In the Arterial Revascularization Trial, off-pump surgery long term outcomes were comparable to those of on-pump; this was not influenced by the use of single vs. bilateral internal thoracic artery.

Perspective Statement:

Off-pump surgery in experienced hands can achieve long term outcomes comparable to those observed after on-pump surgery and therefore off-pump should be considered a valid alternative to on-pump to reduce surgical morbidity following coronary bypass surgery. The choice of bilateral vs. single internal thoracic artery grafts should not influence the decision to adopt the off-pump technique.

Abbreviated legend for Central Picture:

Cumulative outcome incidence in the matched sample in the off-pump vs on-pump groups.

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Figure Legend

Figure 1. Mirrored histogram showing propensity score distribution in the off-pump vs on-pump groups before (white) and after (blue and red respectively) matching.

Figure 2. Cumulative incidence of all-cause death (left) and the composite of all-cause death, myocardial infarction (MI), stroke and revascularization (right) in the matched sample in the off-pump vs on-pump groups.

Figure 3. Cumulative incidence of cardiovascular (CV) death, myocardial infarction (MI), stroke and revascularization in the matched sample in the off-pump vs on-pump groups.

Figure 4. Cumulative incidence of all-cause death (left) and the composite of all-cause death, myocardial infarction (MI), stroke and revascularization (right) in the matched sample in the off-pump vs on-pump groups stratified for the use of single vs bilateral internal thoracic artery (SITA vs. BITA) grafts.

Table 1. Baseline characteristics in the off-pump and on-pump group (matched sample)

	Off-pump surgery	On-pump surgery	P-value	SMD
n	1078	1078		
Age year, mean (sd)	63.83 (8.88)	63.97 (8.74)	0.71	0.02
Female n(%)	144 (13.4)	139 (12.9)	0.79	0.01
Ethnicity n(%)			0.08	0.09
Caucasian	1001 (92.9)	1023 (94.9)		
East Asian	1 (0.1)	4 (0.4)		
South Asian	63 (5.8)	41 (3.8)		
Afro-Carribean	0 (0.0)	2 (0.2)		
African	0 (0.0)	4 (0.4)		
Other	13 (1.2)	4 (0.4)		
Body Mass Index, mean (sd)	28.22 (4.18)	28.33 (3.91)	0.51	0.02
Serum Creatinine mmol/l, mean (sd)	99.07 (20.02)	97.86 (21.93)	0.18	0.05
Unstable Angina n(%)	83 (7.7)	71 (6.6)	0.35	0.04
Treated Hypertension n(%)	813 (75.4)	824 (76.4)	0.61	0.02
Treated Hyperlipaemia n(%)	1012 (93.9)	1019 (94.5)	0.58	0.03
Diabetes n(%)			0.59	0.04
No	850 (78.8)	847 (78.6)		
Insulin Dependent	51 (4.7)	61 (5.7)		
Non-Insulin Depended	177 (16.4)	170 (15.8)		
Smoking n(%)			0.31	0.05
Current smoker	157 (14.6)	136 (12.6)		
Ex-smoker	585 (54.3)	642 (59.6)		
Never	336 (31.2)	300 (27.8)		
COPD n(%)	28 (2.6)	30 (2.8)	0.89	0.01
Asthma n(%)	53 (4.9)	53 (4.9)	1	<0.001
Extracardiac arteriopathy n(%)	72 (6.7)	68 (6.3)	0.79	0.01
Stroke n(%)	29 (2.7)	23 (2.1)	0.48	0.03
Myocardial infarction n(%)	435 (40.4)	450 (41.7)	0.54	0.02
PCI n(%)	182 (16.9)	190 (17.6)	0.69	0.02
History of AF n(%)	15 (1.4)	15 (1.4)	1	<0.001
LVEF n(%)			0.30	0.03
≥50%(good)	842 (78.1)	811 (75.2)		
31-49% (moderate)	205 (19.0)	253 (23.5)		
≤30% (poor)	31 (2.9)	14 (1.3)		
APLT within 3 days n(%)	156 (14.5)	166 (15.4)	0.58	0.02
RCA disease n(%)	695 (64.5)	703 (65.2)	0.75	0.02
Mean vessel quality (1 good, 2 moderate, 3 poor) mean (sd)	1.73 (0.59)	1.69 (0.54)	0.11	0.07
Endarterectomy n(%)	12 (1.1)	14 (1.3)	0.84	0.02
BITA n(%)	497 (46.1)	483 (44.8)	0.57	0.03
Radial artery usage n(%)	224 (20.8)	223 (20.7)	1	0.002
Saphenous vein graft n(%)	804 (74.6)	815 (75.6)	0.61	0.02

COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; AF: atrial fibrillation; LEFT: left ventricular ejection fraction, APLT: antiplatelet therapy; RCA: right coronary artery; BITA: bilateral internal thoracic arterial

Table 2. Hospital outcomes in the off-pump and on-pump group (matched sample)

	Off-pump surgery	On-pump surgery	P-value
	1078	1078	
n grafts	3.21 (0.89)	3.10 (0.79)	0.88
Conversion	27 (2.5)		
Red Blood Cell transfusion n(%)	107 (10.1)	138 (13.2)	**0.04**
Re-exploration n(%)	32 (3.0)	41 (3.8)	0.34
Need for IABP n(%)	50 (4.6)	42 (3.9)	0.45
Renal Replacement Therapy n(%)	61 (5.7)	58 (5.4)	0.85
Acute Kidney Injury n(%)	179 (17.4)	174 (17.1)	0.90
Creatinine peak at 48 hours mmol/l, mean (sd)	111 (44)	107 (61)	0.18
CK-MB at 24 hours, U/Lmean (sd)	36(194)	78(122)	0.06
Troponin at 24 hours U/L mean (sd)	6.5 (24)	7.5 (61)	0.85
Sternal Wound Complication n(%)	30 (2.8)	45 (4.2)	0.10
Death n(%)	9 (0.8)	12 (1.1)	0.66
Myocardial Infarction n(%)	10 (0.9)	28 (2.6)	**0.01**
Stroke n(%)	14 (1.3)	15 (1.4)	1
Repeat Revascularization n(%)	7 (0.6)	6 (0.6)	1
Postoperative atrial fibrillation n(%)	247 (22.9)	295 (27.4)	**0.02**

IABP: intra-aortic balloon pump

Table 3. 10-year outcomes in the off-pump and on-pump group (matched sample)

	Off-pump Surgery	On-pump Surgery	PSM-model only		PSM-model + medication at discharge	
N	1078	1078	HR [95%]	P-value	HR [95%]	P-value
All-cause death n(%)	232 (21.5)	215 (19.9)	1.1[0.84-1.4]	0.54	1.25[0.98.1.6]	0.07
Cardiovascular death n(%)	90 (8.3)	70 (6.5)	0.97[0.57-1.6]	0.91	1.07[0.61-1.8]	0.82
MI n(%)	49 (4.5)	64 (5.9)	0.78[0.53-1.2]	0.21	0.79[0.51-1.2]	0.28
Stroke n(%)	50 (4.6)	47 (4.4)	1.2[0.45-1.5]	0.52	0.95[0.47-1.9]	0.88
Revascularization n(%)	114 (10.6)	111 (10.3)	0.75[0.47-1.2]	0.21	0.70[0.44-1.1]	0.10
Death/MI/stroke/revascularization n(%)	353 (32.7)	356 (33.0)	0.92[0.72-1.2]	0.47	0.95[0.75-1.2]	0.66

PSM: propensity score matching; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction

Table 4. 10-year outcomes in the off-pump and on-pump group in the matched sample stratified for single vs bilateral internal thoracic artery (SITA vs. BITA) grafts with treatment effect and interaction term analysis for outcomes of interest.

	SITA grafting			BITA grafting			
	Off-pump Surgery	On-pump Surgery	HR [95%CI]	Off-pump Surgery	On-pump Surgery	HR [95%CI]	Interaction P
n	581	595		497	483		
All-cause death n(%)	136 (23.4)	125 (21.0)	1.2[0.84-1.8]	96 (19.3)	90 (18.6)	1.1[0.74-1.7]	0.68
Cardiovascular death n(%)	54 (9.3)	39 (6.6)	2[1.1-3.7]	36 (7.2)	31 (6.4)	1[0.45-2.3]	0.21
MI n(%)	28 (4.8)	32 (5.4)	0.89[0.34-2.4]	21 (4.2)	32 (6.6)	0.77[0.34-1.8]	0.82
Stroke n(%)	34 (5.9)	29 (4.9)	1.1[0.46-2.4]	16 (3.2)	18 (3.7)	0.78[0.29-2.1]	0.68
Revascularization n(%)	66 (11.4)	54 (9.1)	1.1[0.68-1.9]	48 (9.7)	57 (11.8)	0.75[0.41-1.4]	0.27
Death/MI/stroke/revascularization n(%)	204 (35.1)	199 (33.4)	1[0.72-1.5]	149 (30.0)	157 (32.5)	0.9[0.63-1.3]	0.41

HR: hazard ratio; CI: confidence interval; SITA: single internal thoracic artery; BITA: bilateral internal thoracic arteries; MI: Myocardial infarction